

**PROGNOSTIC VALUE OF THE PERSISTENCE OR CHANGE IN PERICARDIAL
EFFUSION STATUS ON SERIAL ECHOCARDIOGRAMS IN PULMONARY
ARTERIAL HYPERTENSION**

by

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Zeina Abdulrazzak Dardari, M.S.

Abstract:

Background: Pericardial effusion in pulmonary arterial hypertension (PAH) is an indicator of right heart failure and a marker of poor prognosis; its significance on serial transthoracic echocardiograms (TTE) is not clear.

Methods: We examined our database for PAH patients followed at our center (10/99-11/07). Baseline and follow-up TTE (1.0 ± 0.5 y) and outcomes were studied (N=200). The presence of pericardial effusion was evaluated at baseline and follow-up. The persistence or change in pericardial effusion status was categorized into four categories. Kaplan Meier methods were used to estimate survival functions of the various categories. Cox proportional hazards modeling was used to adjust for other covariates and identify independent predictors.

Results: Over a mean follow-up of 4.6 ± 2.6 y, 53% (n=106) patients died. Pericardial effusion was present in 20% (n=40) at baseline and 22% (n=44) during follow up. Patients with pericardial effusion at baseline or follow-up had significantly higher creatinine, pulmonary vascular resistance, lower cardiac output, and were more likely to be treated with prostanoids. During follow-up, there was significantly increased prostanoids (58% vs. 28%) and combination therapy (8% vs. 2%) use compared to baseline. New or persistence of pericardial effusion was associated with worse outcomes ($p < 0.001$) and an independent predictor of survival after adjusting for age, creatinine, sodium, cardiac output, mean right atrial pressure, New York Heart

Association (NYHA) functional class, and presence of connective tissue disease as the etiology of PAH (p-value<0.001).

Conclusion: New or persistent pericardial effusion in PAH despite vasoactive therapy predicts worse outcomes; absence or resolution of pericardial effusion with therapy suggests better prognosis. Its public health significance is the ability to identify patients that may benefit from closer follow-up for reassessment and consideration of more aggressive medical therapy or referral for lung transplant to prevent worsening health and/or death.

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LIST OF ABBREVIATIONS

BMI=Body Mass Index
CAD=Coronary Artery Disease
CHD=Congenital Heart Disease
CI=Cardiac Index
CKD=Chronic Kidney Disease
CO=Cardiac Output
COPD=Chronic Obstructive Pulmonary Disease
CTD=Connective Tissue Disease
DIFFEFF=Difference In Effusion Status
DM=Diabetes Mellitus
ETB=Endothelin Blocker
FPAH=Familial Pulmonary Arterial Disease
HLP=Hyper Lipidemia
HTN=Hypertension
IPAH=Idiopathic Pulmonary Arterial Disease
NYHA=New York Heart Association
OSA=Obstructive Sleep Apnea
PA=Pulmonary Artery
PAH=Pulmonary Arterial Hypertension
PH= Pulmonary Hypertension
PTE5=Phosphodiesterase Type 5
PVR=Pulmonary Vascular Resistance
RA=Right Arterial
RV=Right Ventricle
TTE=Trans Thoracic Echocardiogram

1.0 INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease caused by a pathologic increase in pulmonary vascular resistance leading to progressive right ventricular (RV) failure and death (1-6). Pericardial effusion in the presence of PAH is associated with worse right-sided cardiac hemodynamics and RV decompensation, and is a predictor of worse outcomes (7-13). Data about the significance of pericardial effusion during follow-up is limited (14). Furthermore, the significance of resolution versus persistence of pericardial effusion on serial echocardiograms has not been described. We hypothesized that the presence or persistence of pericardial effusion during follow-up is associated with RV dysfunction and decreased survival.

1.1 PULMONARY ARTERIAL HYPERTENSION

PAH is a condition where the pulmonary arteries become restrictive to blood flow through the lungs, leading to elevated right heart pressures (1). The right side of the heart pumps blood into the lungs to collect oxygen and expel carbon dioxide. After the exchange has taken place, the blood is returned to the left side of the heart where it is pumped out to the rest of the body. Because of the increased resistance to blood flow in the pulmonary arteries in PAH, the right side of the heart has to pump harder in order to force the blood to pass through the lungs. This causes the right side of the heart to become enlarged overtime and eventually leads to right heart failure and death. (1-2)

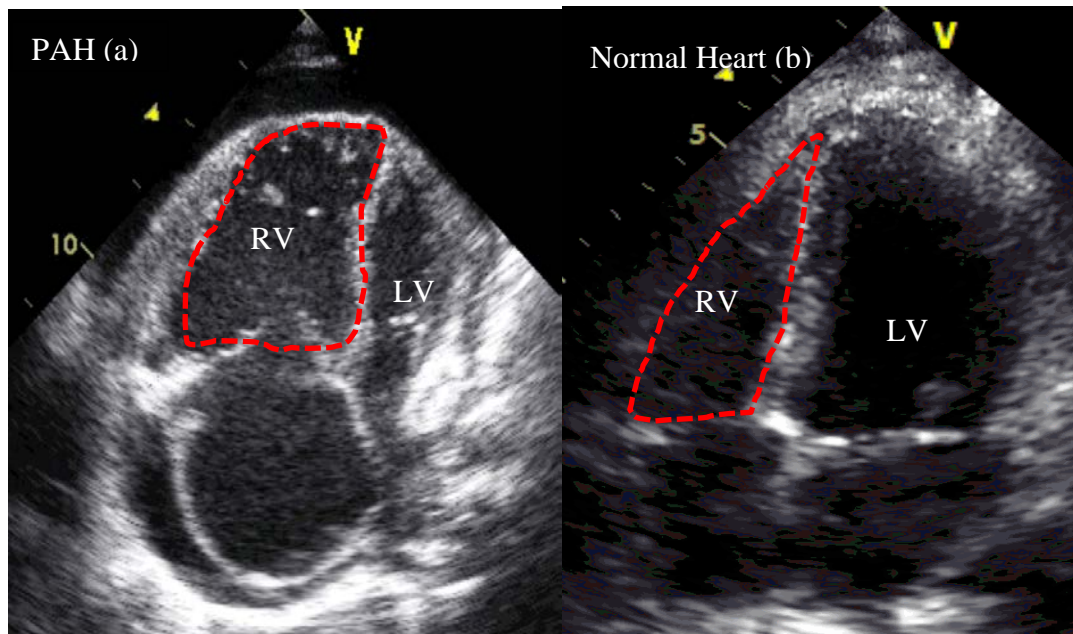


Figure 1: Pulmonary Arterial Hypertension (a) versus Normal Heart (b).

Notice, in figure one, how the right ventricle (RV) is much larger than the left ventricle (LV) in the patient with pulmonary arterial hypertension (PAH).

PAH may be a result of an unknown cause (idiopathic PAH), inherited (familial PAH), due to birth defects of the heart, liver disease, connective tissue disease, HIV infection, certain medications, or other rare conditions (associated PAH). To confirm diagnoses of PAH, patients undergo a detailed examination by the physician and are referred for several tests including a chest X-ray, computed tomography (CT) scan, transthoracic echocardiogram (TTE), ventilation perfusion scan, sleep study, several blood tests, and right heart cardiac catheterization to directly measure hemodynamics (the right heart pressures and cardiac output)(15).

1.2 PERICARDIAL EFFUSION

Pericardial effusion refers to fluid that accumulates in the pericardial space (a double layered sac that surrounds the heart), and can be detected by using a TTE. Drainage of this fluid is referred to as pericardiocentesis. Notice that in figure 2 the presence of pericardial effusion (a) versus a normal heart (b).

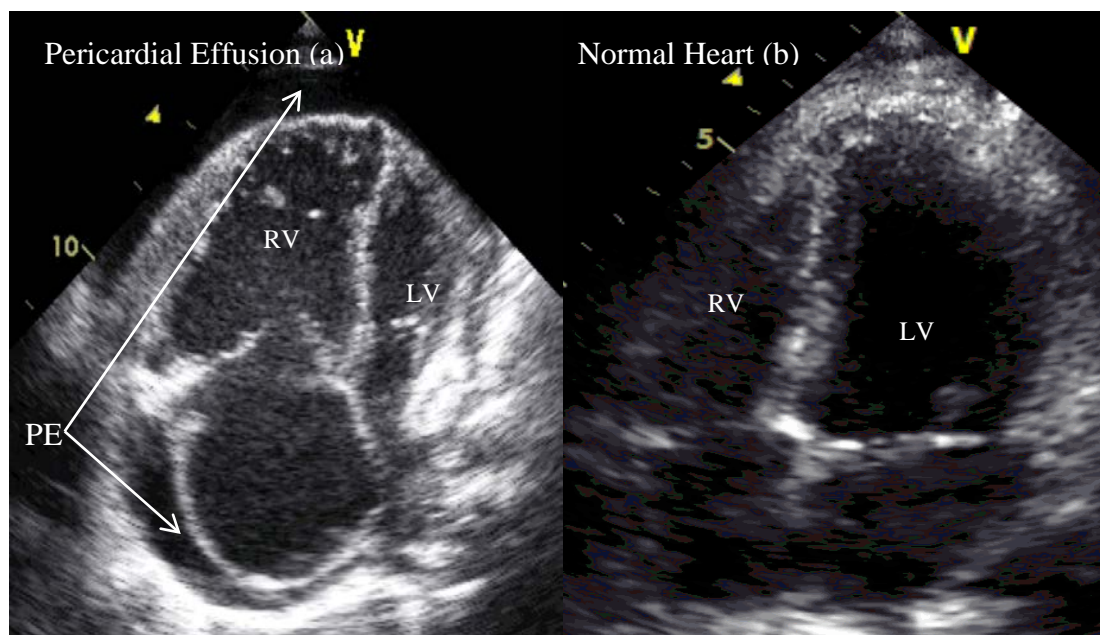


Figure 2: Illustration of (a) Heart with Pericardial Effusion (PE) versus (b) Normal Heart.

1.3 SIGNIFICANCE OF RESEARCH

While presence of pericardial effusion in patients with PAH has been associated with poor prognosis, the significance of evolution of pericardial effusion in patients on PAH therapy over time is unclear. We believe that patients who do not have a pericardial effusion at both baseline and follow-up, represent a lower risk group; versus, patients who have a pericardial effusion that persists or develops during follow-up. Such information would be useful to identify patients that may benefit from closer follow-up for reassessment and consideration of more aggressive medical therapy or referral for lung transplant to prevent getting worse or death.

2.0 MATERIALS AND METHODS

2.1 THE STUDY POPULATION

2.1.1 Sample Selection

We conducted a retrospective cohort study by reviewing medical records of patients with PAH at the University of Pittsburgh Medical Center (UPMC) in Pittsburgh, Pennsylvania. The World Health Organization classifies pulmonary hypertension (PH) into five groups based on the underlying cause of PH. Our study population was limited to only patients with group 1 pulmonary arterial hypertension (PAH) as per the Dana Point's clinical classification version (16). Our initial sample of 503 patients was collected from UPMC's pulmonary hypertension registry from October 1999 to November 2008. One hundred twenty six patients had no TTEs performed during the study period and were excluded. Six patients were not found to have pulmonary hypertension after diagnostic evaluation, and were excluded from the study. An additional 83 patients were not considered PAH patient and were also excluded. There were 15 patients who had a heart or lung transplant before 1999 were excluded from the study. The study protocol also required that least two TTEs were performed during the years 1999-2008. Consequently, 73 patients with no follow-up TTE in the study period were excluded from the study leaving a final sample size of 200 patients. Figure 3 illustrates the derivation of the final sample.

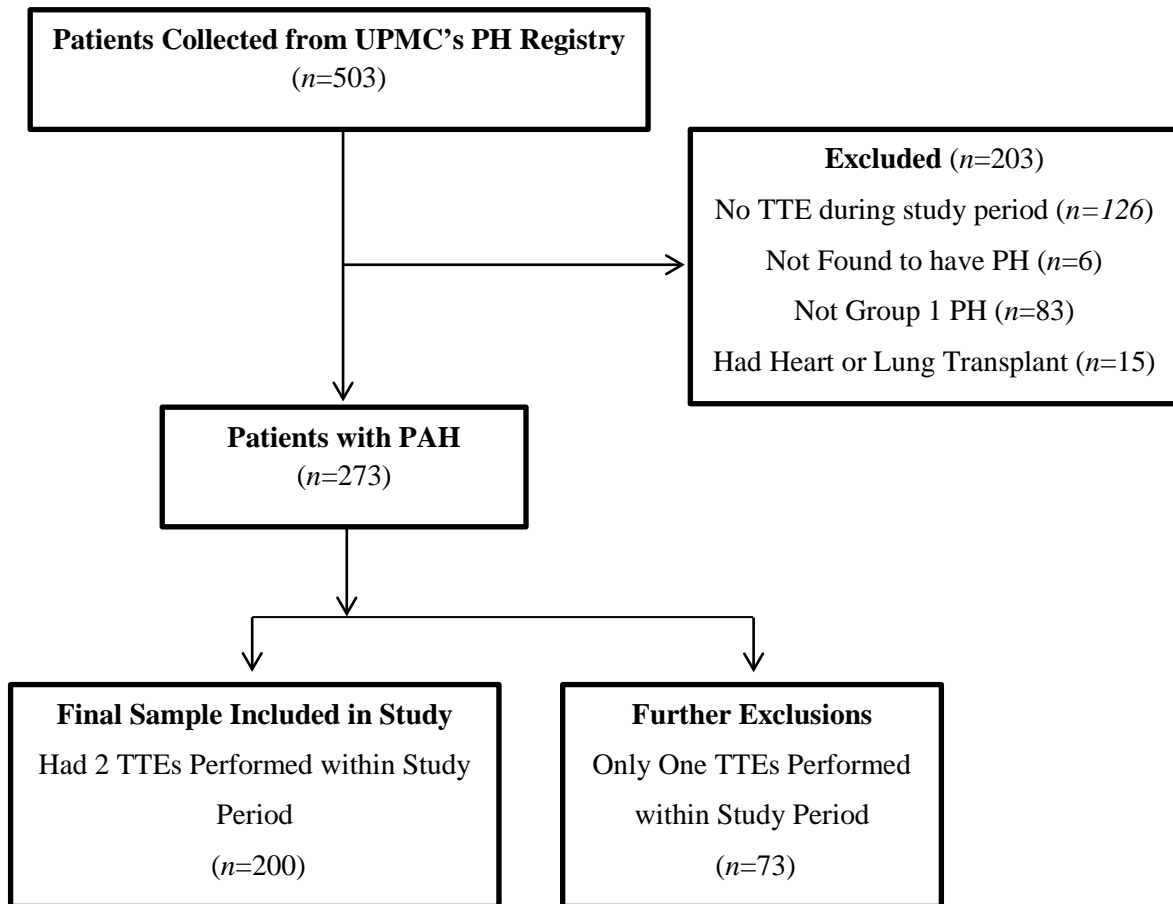


Figure 3: Flow Chart of Final Sample Selection

2.1.2 Selection of TTEs

The first TTE that was performed during years 1999-2007 was selected as each patient's baseline TTE measurement. We then selected a second TTE such that it was performed approximately one year from the baseline TTE.

2.2 STUDY VARIABLES

2.2.1 Descriptive Variables

Table 1 depicts our study variables. Demographics, clinical characteristics, pulmonary function tests, and serum biomarker data were collected at baseline. PAH medications, functional status and echocardiographic variables were determined at baseline and at the time of the second TTE. Hemodynamics was determined approximately 6 months from baseline.

Table 1: List of Study Variables

Demographics	PAH Medications
Age	Combination Medications
BMI	ET Blocker
Female	No Medication
Caucasian	Prostanoid
Clinical Characteristics	PTE5 Inhibitor
Coronary Artery Disease	Echo Measurements
Chronic Kidney Disease	Pericardial effusion
Chronic Obstructive Pulmonary Disease	Functional Status
Diabetes Mellitus	New York Heart Association
Hyper Lipidemia	Hemodynamics
Hypertension	Fick Cardiac Index
Obstructive Sleep Apnea	Fick Cardiac Output
Smoking history	Pulmonary Artery Mean Pressure
Etiology PAH	Right Arterial Mean Pressure
Congenital Heart Disease	Pulmonary Vascular Resistance
Cirrhosis	Serum Biomarker
Connective Tissue Disease	Albumin
Familial Pulmonary Arterial Disease	Creatinine
Idiopathic Pulmonary Arterial Disease	
Phen Phen	

2.2.2 Pericardial Effusion Status

The focus of our study was the persistence or change in pericardial effusion status from baseline to an approximate one year follow-up date. In order to categorize this event we created a variable called Difference in Pericardial Effusion from Baseline to One Year Follow-up (DIFFEFF). Table 2 shows definition of each category of this variable.

We hypothesized that this categorization would be ordinal with the reasoning that a person with no pericardial effusion (category 1) would be medically best off, whereas one whose pericardial effusion disappears at follow-up (category 2) is better off than a person who instead develops one at follow-up (category 3). Furthermore, we reasoned that a person who has had a pericardial effusion at both baseline and follow-up (category 4) is worse off than a person who recently developed it at follow-up (category 3). We hypothesized that persistence of pericardial effusion over time despite PAH therapy, reflects worse disease severity that is not responding to treatment.

Table 2: Definition of the Variable Difference in Pericardial Effusion from Baseline to One Year Follow-up (DIFFEFF)

Value	Presence of Pericardial Effusion	
	TTE 1	TTE 2
1	Not Present	Not Present
2	Present	Not Present
3	Not Present	Present
4	Present	Present

2.3 STATISTICAL METHODS

2.3.1 Survival Analysis

The main focus of our study was to compare the estimated survival among the difference categories of DIFFEFF. We set up our survival problem such that the time of origin for each patient was to be the date of their baseline TTE. Furthermore, the event of interest to be observed was death. We followed patients starting from their baseline TTE up until death or January 2012; whichever came first. Patients surviving beyond January 2012 were considered to be right censored. Death was verified using patient medical records and the social security death index.

2.3.2 Survival Model

We used The Kaplan–Meier procedure was used to estimate the survival function of each category of DIFFEFF. A test of trend was used to determine whether there was a systematic difference among the survival distributions of each category. A p-value <0.05 from the test of trend was used to indicate a significant trend among the survival curves. We also tested the proportional hazards assumption based on the four survival curves. A p-value <0.05 would indicate that the proportional hazards assumption had been violated. A Cox proportional hazard model was then built including several covariates to reduce variability and/or to control for confounding. Potential covariates were preselected based on principle investigator's knowledge of potential confounding issues. Confounding variables included age, creatinine, fick cardiac output, connective tissue disease, mean right arterial pressure, NYHA functional class, and sodium.

2.3.2 Distributional Tests

Chi-square analysis was used to compare differences between groups, in proportions of categorical variables. Two sample t-tests were used to compare means between groups for normally distributed continuous variables. Kruskal-Wallis equality of population rank tests were used to compare distributions between groups, of non-normally distributed continuous variables.

3.0 RESULTS

3.1 DESCRIPTIVES OF SAMPLE

In order to understand our sample, table 3 shows the Demographics and Clinical Characteristics of the sample at baseline.

Table 3: Clinical Characteristics of 200 Patients at Baseline

Demographics		
Age	54.1 \pm 14.7	
BMI	29.4 \pm 9.0	
Female	90.9%	180
Caucasian	70.5%	141
Comorbidities		
Coronary Artery Disease	14%	28
Chronic Kidney Disease	11.5%	23
Chronic Obstructive Pulmonary Disease	14%	28
Diabetes Mellitus	14.5%	29
Hyper Lipidemia	24.5%	49
Hypertension	42.2%	84
Obstructive Sleep Apnea	15%	30
History of Smoking	46%	92
Etiology PAH		
Congenital Heart Disease	11.1%	22
Cirrhosis	7.1%	14
Connective Tissue Disease	33.3%	66
Familial Pulmonary Arterial Disease	1.0%	2
Idiopathic Pulmonary Arterial Disease	46.5%	92
Phen Phen	1.0%	2

Data for continuous variables are presented as mean \pm standard deviation and values for categorical values are presented as the total number and the percent of subjects with that certain attribute. All estimates are based on N=200 excluding BMI where N=187.

In order to determine what clinical characteristics may be associated with patients with a pericardial effusion and those without one, we compared the two groups. Table 4 shows the distribution of select certain clinical characteristics between individuals who had a pericardial effusion either at baseline and/or follow-up versus those who never had a pericardial effusion at either time point. We can see that creatinine is significantly higher in individuals who had a pericardial effusion (p-value <0.001). Also the percentage of individual who have connective tissue disease is higher in individuals who had a pericardial effusion present at either time point. Moreover, individuals who did not have a pericardial effusion at either baseline and/or follow-up had lower mean right atrial pressure and pulmonary vascular resistance, and higher fick cardiac output.

Table 4: Results of Comparison of Selected Variables: Individuals who had a Pericardial Effusion Present at TTE1 and/or TTE2 versus those who had No Pericardial Effusion Present at either.

Variable	All patients	No pericardial effusion at TTE1 or TTE2 (N=142)	Pericardial effusion present at TTE1 or TTE2 (N=58)	p-value
Demographics				
Age (y)	54 ± 15	54 ± 15	55 ± 13	0.7
Female (%)	71	68	76	0.3
Caucasian (%)	91	92	89	0.4
BMI (Kg/m ²)	29 ± 9	29 ± 9	30 ± 10	0.6
Creatinine (mg/dl)	1.1 ± 0.6	1.0 ± 0.5	1.3 ± 0.7	0.0003
NYHA at TTE1	2.5 ± 0.7	2.4 ± 0.7	2.5 ± 0.8	0.8
NYHA at TTE2	2.4 ± 0.8	2.4 ± 0.7	2.5 ± 0.9	0.2
IPAH (%)	47	49	43	0.2
CTD (%)	33	26	50	0.001
Hemodynamics				
RA mean (mmHg)	10 ± 8	9.2±8.8	11.1±5.6	0.007
PA mean (mmHg)	48 ± 16	48 ± 17	51 ± 14	0.2
Fick CO1 (L/min)	5.1 ± 1.9	5.4 ± 1.9	4.6 ± 1.8	0.006
PVR (Wood units)	8 ± 6	7 ± 6	11 ± 7	0.0003

Data for continuous variables are presented as mean ± standard deviation and values for categorical values are presented as the total number and the percent of subjects with that certain attribute

It is important to understand how patients are being treated for PAH because the final results we are trying to reach is to determine the prognostic significance of the persistence or change in pericardial effusion status from baseline to follow-up despite vasoactive therapy for the treatment of PAH. Table 5 shows the frequency and percentage of individuals on different medications or if they are on a combination of medications. The table also shows the New York Heart Association (NYHA) functional status of the 200 individuals in our study. We can see that the percentage of individuals taking Prostanoids, PTE5 Inhibitors, ET Blockers, Calcium Channel Blockers, and a combination of medications increased from baseline to follow-up. As a result, the percentage of individuals taking no medications has significantly decreased. NYHA however, appears to have remained the same from baseline to follow-up.

Table 5: Pulmonary Arterial Hypertension Medications and Functional Status of 200 Patients at Baseline and One Year Follow-up

PAH Medications		Baseline		Follow-up	
Medications					
Prostanoid		28.1%	56	41.5%	83
PTE5 Inhibitor		5.5%	11	19.5%	39
ET Blocker		37.2%	74	52.3%	104
Calcium Chanel Blocker		24.5%	49	27.0%	54
Combination of Medications		2.5%	5	7.5%	15
No Medications		27%	54	7.5%	15
Functional Status					
NYHA		2.44± .749		2.41±.786	

Data for continuous variables are presented as mean ± standard deviation and values for medications are presented as the total number and percent of subjects with that certain medication; Estimates are based on N=200.

Table 6 shows the mean time from an approximate date of diagnosis of PAH to the first TTE (baseline) in 148 patients. We looked at this time difference in order to get a sense of how long patients have had PAH and to determine that one category of DIFFEFF hasn't on average had PAH longer. The overall mean time is 2.4 years with a standard deviation of 2.6 years. The Kruskal-Wallis test of equality of populations rank test indicated that the mean times do not differ (p-value=0.14) across the DIFFEFF categories.

Table 6: Description of Time (years) between an Approximate Diagnosis of PAH and Baseline TTE across DIFFEFF Categories

DIFFEFF Categories*	Mean	SD	Minimum	Median	Maximum
(1) Not Present/ Not Present	2.7	2.7	0	2.1	10.9
(2) Present/ Not present	1.5	2.5	0	0.1	8.4
(3) Not Present/Present	1.8	2.0	0	1.1	6.0
(4) Present/ Present	2.0	2.0	0	1.7	7.4
Overall	2.4	2.6	0	1.7	10.9

*Kruskal-Wallis equality of populations rank test across DIFFEFF (p-value=0.14); Time values are presented in years; SD=Standard Deviation.; Estimates are based on N=147 (26.5% Missing); DIFFEFF = Difference in Pericardial Effusion from Baseline to One Year Follow-up.

In our study, the selection of baseline and follow-up TTEs was done such that on average we have a one year follow-up period to observe any change in the status of pericardial effusion. In Table 7, we described the average time between baseline TTE and follow-up TTE across the different categories of DIFFEFF. The average follow-up appears to be very similar across the categories with the highest mean follow-up time being 385.9 days and the lowest mean follow-up time being 354.6 days. Overall, it appears that the average time between baseline TTE and follow-up TTE is 377 days (approximately 1 year).

Table 7: Description of Time between Baseline and Follow-up Echoes across DIFFEFF Categories

DIFFEFF Categories*	Mean	SD	Minimum	Median	Maximum
(1) Not Present/ Not Present	381.2	183.2	76	354.5	1491
(2) Present/ Not present	354.6	141.8	132	358	716
(3) Not Present/Present	385.9	195	174	357	934
(4) Present/ Present	363.4	116.0	134	365	658
Overall	377.4	173.6	76	357	1491

*Kruskal-Wallis equality of populations rank test across DIFFEFF (p-value= 0.97); Time values are presented in days; SD=Standard Deviation.; Estimates are based on N=200; DIFFEFF = Difference in Pericardial Effusion from Baseline to One Year Follow-up.

3.2 SURVIVAL ANALYSIS

3.2.1 Survival Data

According to Table 8, the minimum time an individual was followed until they died or were considered censored was 0.3 years. On the other hand, the maximum time an individual was followed up until they died or were censored was 11.6 years. Overall, 53% of individuals in our study died during the study period. Individuals with a pericardial effusion at both baseline and follow-up had the highest percentage (80%) of deaths compared to the other categories. Moreover, individuals who had developed a pericardial effusion during follow-up had the second highest percentage of deaths (61.1%) when compared to the other categories. Both individuals who never had a pericardial effusion or who had one at baseline and then the pericardial effusion resolved at follow-up, have similar percentages of death (47.9% & 47.7%).

Table 8: Description of Survival Data across DIFFEFF Categories

DIFFEFF Categories	Number of Subjects	Observed Deaths	Time of Follow-up				
			Mean	SD	Minimum	Median	Maximum
(1) Not Present/ Not Present	142	68	5.0	2.4	0.3	5.4	11.6
(2) Present/ Not present	15	7	4.8	2.7	1	5.5	8.6
(3) Not Present/Present	18	11	4.2	3.1	1.1	3.2	11.4
(4) Present/ Present	25	20	2.5	1.8	0.4	1.6	6.5
Overall	200	106	4.6	2.6	0.3	4.7	11.6

Time values are presented in years; SD=Standard Deviation. Estimates are based on N=200; DIFFEFF = Difference in Pericardial Effusion from Baseline to One Year Follow-up.

Tables 9 shows the number of individuals at risk at baseline (time=0), at 5 years, and at 10 years. Just to note that time of origin for each individual starts as soon as they entered the study, some being later in the study period than others. As a result, some individuals were censored sooner.

Table 9: Number of Individuals at Risk across DIFFEFF Categories:
Time =0, 5, 10 years

DIFFEFF Categories	Time (years)		
	0	5	10
(1) Not Present/ Not Present	142	77	2
(2) Present/ Not present	15	9	0
(3) Not Present/Present	18	6	1
(4) Present/ Present	25	3	0

DIFFEFF = Difference in Pericardial Effusion from Baseline to One Year Follow-up.

3.2.2 Univariable Survival Analysis

According to the results of the Kaplan Meier survival curve and the univariable proportional hazards model (Figure 3 & Table 10), it appears that individuals whose pericardial effusion resolves (disappears), do as well as those who never had a pericardial effusion present during the initial 1 year period. Furthermore, it appears that individuals who develop a pericardial effusion at follow-up may do as well as those individuals never having a pericardial effusion present (hazards ratio=1.6 p-value=0.1). Finally, we can see that individuals who have a pericardial effusion present at both baseline and follow-up do much worse than those individuals who never had a pericardial effusion at either time point (hazards ratio=3.5 p-value=<0.001). Over all, the test of trend indicated that there is a significant trend among the categories (p-value <0.001). This trend may be more prominent in an adjusted model.

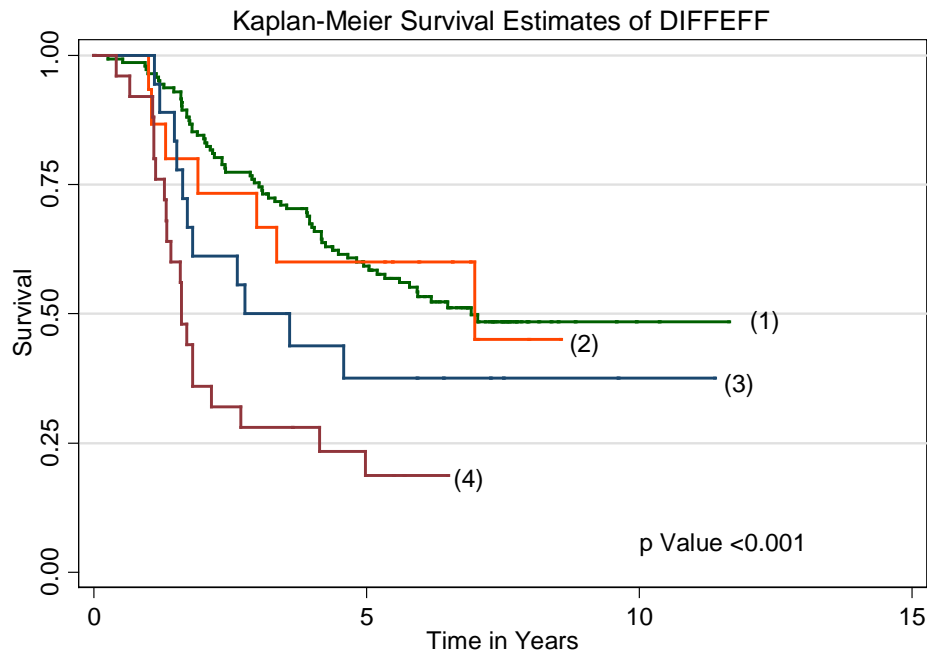


Figure 4: Kaplan Meier survival curves for different categories of Difference in Pericardial Effusion from Baseline to One Year Follow-up (DIFFEFF). *P-Value is based on test of trend for the survival functions.

Table 10: Results of Univariable Cox Proportional Hazards Model: Hazards Ratios, 95% Confidence Interval, and p Values for Difference in Pericardial Effusion from Baseline to One Year Follow-up (DIFFEFF)

DIFFEFF Categories	Hazard Ratio (95% CI)	p Value
(1) Not Present/ Not Present	Reference Category	-
(2) Present/ Not Present	1.0 (0.5-2.2)	0.9
(3) Not Present/Present	1.6 (0.9-3.1)	0.1
(4) Present/ Present	3.5 (2.1-5.8)	<0.001

CI = Confidence Interval; DIFFEFF = Difference in Pericardial Effusion from Baseline to One Year Follow-up.

3.2.3 Multivariable Survival Analysis

In order to control for potential confounding variables, we built a multivariable model including DIFFEFF as well as age, creatinine, Fick cardiac output, connective tissues disease, mean RA pressure, NYHA functional class, and sodium. When controlling for the confounding variables, we can see that individuals who developed a pericardial effusion at follow-up, do significantly worse than those who never had a pericardial effusion at either time point (hazards ratio=2.3 p-value=0.03) (Table 11). Also, individuals who had a pericardial effusion present at both baseline and follow-up also do much worse than those who never had a pericardial effusion at either time point (hazards ratio=3.0 p-value=<0.01).

Table 11: Results of Multivariable Cox Proportional Hazards Model: Hazards Ratios, 95% Confidence Interval, and P-values

Variables	Hazards Ratio	95% CI	P-value
DIFFEFF*			
(2) Present/ Not present	0.9	0.34-2.3	0.8
(3) Not Present/Present	2.3	1.07-5.15	0.03
(4) Present/ Present	3.0	1.49-6.15	<0.01
Age	1.0	0.99-1.02	0.5
Creatinine	1.4	0.95-1.92	0.1
Fick Cardiac Output	1.0	0.90-1.15	0.8
Connective Tissue Disease	1.2	0.73-2.04	0.45
Mean RA Pressure	1.0	0.99-1.04	0.44
NYHA Functional Class	1.0	0.79-1.45	0.67
Sodium	0.9	0.87-0.97	<0.01

*Baseline Category= (1) Not Present/ Not Present; Overall test of model significance =p-value<0.001. Proportional Hazards Assumption Test P-value=0.3134.

3.3 PERICARDIOCENTESIS

In our study population, 2 patients underwent pericardiocentesis (drainage of fluid from pericardial space). One patient had severe PAH secondary to systemic sclerosis and presented electively for pericardiocentesis of a large effusion. After 670 ml of fluid was removed, she developed respiratory distress and hypotension requiring brief intubation and inotropic support (dobutamine). She was discharged after a weeklong hospitalization and repeat TTE 2 weeks later showed no pericardial effusion. She was alive at the last point of contact within our hospital system 5 years later.

The second patient also had scleroderma and PAH admitted to the hospital with rapid atrial fibrillation and noted to have a large pericardial effusion with evidence of increased pericardial pressures. Consequently 1100 ml of fluid was removed and another 830 ml were drained 2 days later without complications. He was discharged 7 days later with a trivial pericardial effusion. A repeat echocardiogram 1 year later showed no effusion. He died about 3.4 years after initial pericardiocentesis.

3.4 SENSITIVITY ANALYSIS

Our study design was to include patients who had two consecutive TTEs one year apart. We wanted to make conclusions that were based on a one year follow-up period. As we found much variability in the length of time between baseline and follow-up TTEs (e.g., 76 to 1491 days) a more homogeneous subgroup needed to be identified. A subsample of individuals with follow-up times between 10 to 14 months was identified and contained 42% of the patients. We performed a reanalysis using this subsample.

We found that, similar to our original results, individuals who develop a pericardial effusion at follow-up as well as those whose pericardial effusion persists to follow-up, both do significantly worse than individuals who never had a pericardial effusion at either baseline or follow-up. Furthermore, the test of trend was also significant (p-value <0.0001), indicating a systematic difference among the survival distributions of DIFFEFF.

The only difference that was found was in the multivariable model. When adjusting for age, creatinine, sodium, cardiac output, mean right atrial pressure, New York Heart Association (NYHA) functional class, and the presence of connective tissue disease as the etiology of PAH, it was found that category 3 and 4 of DIFFEFF had different hazards ratios when compared to our original results. To address this issue, we went back to our original sample and tested whether or not categories 3 and 4 were significantly different from each other. It was found that they did not differ (p-value=0.09). We then tested it again in our sub-sample, and also they were not found to differ.

We can conclude that by limiting our sample to individuals who had follow-up periods greater than or equal to 10 months and less than or equal to 14 months, we also get results similar to that of our original sample.

4.0 DISCUSSION

This study shows that pericardial effusion is common during management of patients diagnosed with PAH and is prognostically significant. It is the first study to show that pericardial effusion in PAH patients is dynamic and this change in pericardial effusion over time is important in regards to survival.

Pericardial effusion in PAH has been consistently found to be a predictor of decreased survival (7-14). Recently, the appearance of new pericardial effusion in PAH patients have been also found to be prognostically significant in a single center retrospective study (14), and our study is consistent with these findings. In our study, we assessed patients by TTE at two time points from the time of initial diagnosis of PAH and found that the presence of pericardial effusion was a predictor of mortality at both time points. Furthermore, the change in pericardial effusion derived by considering both the time points of TTE 1 and 2 revealed the most useful prognostic information which remained independently predictive in a model that also includes age, creatinine, sodium, cardiac output, mean right atrial pressure, NYHA functional class, and presence of connective tissue disease as the etiology of PAH. Currently, guidelines for longitudinal assessment of patients with established PAH are lacking (1). Our study suggests that pericardial effusion may be a potential marker for assessing PAH patients over time, but this will need confirmation in larger prospective studies.

Pericardiocentesis for a large effusion was performed in 2 patients in our study, one of whom had to be admitted to the coronary care unit for hypotension and respiratory failure after the procedure, however there were no immediate deaths attributed to the procedure. Pericardiocentesis in the setting of PAH is an uncommon procedure largely due to the notoriously high complication rate (16). As such, management of large effusions has generally been by medical optimization of PAH therapy rather than therapeutic drainage.

Limitations of our study include a retrospective design leading to right heart hemodynamics being unavailable in 15% of patients during the study period. Right heart hemodynamics was also not obtained at the same time of the TTE. The six-minute walk test was not routinely performed during the study period and was therefore not available for analysis. Moreover, information about the date of diagnosis of PAH is unknown in 26% of individuals in our study.

5.0 CONCLUSION

Pericardial effusion is dynamic in patients with PAH and serial follow-up for resolution versus persistence is prognostically valuable and may be a useful marker for the longitudinal follow-up these patients.

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